REMARKS

Claims 1-13 and 50-56, of which claims 1-5 are currently amended and claims 51-56 are new, are pending and appear in this application for the Examiner's review and reconsideration. Claims 14-49 are withdrawn in view of the restriction requirement, but these claims have been amended to depend upon claim 1 so that they can be reinstated and allowed when claim 1 is allowed. Claim 1 is amended for clarification and to distinguish features of the invention over the prior art. Claim 2 is amended to correct an informality. Claims 3-5 are amended for clarification. New claims 51-56 are added to cover preferred embodiments of the invention. Support for these amendments are found in the original claims and throughout the specification. As no new matter is added, entry of the amendments at this time is respectfully requested.

Priority

The Examiner notes that a certified copy of the parent PCT application, filed July 18, 2002, has not been filed as required by 35 U.S.C. § 119(b). However, the PCT application had entered U.S. national stage, and therefore is a U.S. application rather than a priority document. Accordingly, it is believed that a certified copy of the PCT application is not required.

A certified copy of the Israeli Application No. 144446, filed July 19, 2001 and relied on for foreign priority in this application, is submitted herewith. [awaiting this document from client]

Specification

In response to the Examiner's comments on the abstract, a replacement abstract is attached hereto. As required, the replacement abstract is presented on a separate sheet.

The specification is also amended to properly identify the trademarks used in the specification, as the Examiner suggested.

Claim Objections

Claim 1 is objected to because of the informality noted in the Office Action, and is amended to correct the informality. Claim 2 is also amended for clarity as the Examiner suggested.

Claim Rejections -- 35 U.S.C. § 112

Claims 1-13 and 50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter for the reasons stated on pages 4-5 of the Office Action.

In response, claim 1 is amended to clarify that the claim is directed to a fibrin matrix formed by mixing plasma proteins comprising fibrogen, thrombin, Factor XIII, and at least one anti-fibrinolytic agent, in substantial absence of organic chelating agents. Amended claim 1 recites "substantial absence of organic chelating agents" and "substantially regular pores," instead of the recitations "substantially devoid of organic chelating agents" and "substantially uniform pores," respectively, which the Examiner noted as confusing. The recitation "substantial absence of organic chelating agents" is defined in the specification, at page 15, lines 14-15, as referring to a concentration less than 1 mm. The specification also explains the term "substantially regular pores" as meaning that "the majority of the pores or more preferably substantially all pores are in the same size range" (p. 7, lines 12-14). Thus, Applicants respectfully submit that the amended recitations clearly define the subject matter of the claim.

With respect to the Examiner's comments regarding the recitation of "residual moisture" below 3%, Applicants note that the recitation "residual moisture" relates to the trace of water found in freeze-dried (lyophilized) material. The term is well known in the art and is often used in the context of lyophilized products, and also appears in U.S. Patent Nos. 6,293,970 and 6,548,729, which are cited in the Office Action. A guideline for testing residual moisture and copies of representative articles are attached hereto as Exhibit A to further demonstrate common use of the term. Accordingly, Applicants respectfully submit that the meaning of the recitation "residual moisture" is clear as known in the art and evidenced by common usage of the term.

Therefore, the rejection of claim 1 for indefiniteness under § 112, second paragraph should be withdrawn.

The Examiner states that claims 3 and 4 are confusing because no reference point is provided for the term "autologous." Not only is "autologous" a commonly used term that would be readily understood by one skilled in the art, however, but the meaning of the term is explained in the specification, which provides that, in an embodiment of the invention, "blood is drawn from a patient in need of tissue repair or regeneration, plasma proteins are isolated from the autologous plasma and a matrix prepared thereof" (p. 16, lines 13-15). Thus, the specification explains that "autologous" plasma means a plasma derived from a

patient who thereafter receives the matrix. Furthermore, in the interest of expediting the prosecution of this application, claims 3 and 4 are amended to recite that the plasma protein is autologous to a patient in need of the matrix. Thus, the rejection of claims 3 and 4 under § 112 should be withdrawn.

Claim 5 is rejected as confusing because of the recitation "tranexamic acid present in an amount of at least 5%" does not specify the type of the percentage. Claim 5 has been amended to remove this recitation, and this rejection is therefore moot.

Accordingly, all rejections under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claim Rejections -- 35 U.S.C. § 103

Claims 1-13 and 50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,548,729 (Seelich et al.) taken in view of U.S. Patent No. 5,631,011 (Wadstrom), U.S. Patent No. 6,293,970 (Wolfinbarger, Jr., et al.), and U.S. Patent No. 6,090,996 (Li) for the reasons set forth on pages 6-9 of the Office Action. Applicants respectfully traverse.

First, Seelich discloses a fibrin sponge with "a residual moisture content of at least 3%, preferably 3 to 35%, in particular 10-20%" (Abstract). The residual moisture is adjusted to the specified level to provide the fibrin sponge with "a soft and smooth consistency, thereby substantially improving its handling and efficacy" (col. 1, lines 55-62). Example 1 of Seelich, which is cited by the Examiner, discloses a fibrin material with approximately 15% residual moisture. Such high residual moisture is obtained by incubating in a humid chamber to improve softness and pliability of the sponge, which is "hard" and "brittle" at a lower residual moisture level (*see* col. 8, lines 35-46; col. 1, lines 64-67). Thus, an essential feature of the fibrin sponge disclosed in Seelich is its high residual moisture content, which must be *at least 3%* for softness and pliability, in direct contrast to the present fibrin matrix, which contains a residual moisture *below 3%* but is not "hard" or "brittle" as taught in the prior art.

In this respect, the Examiner is incorrect in stating that "the selection of the degree of residual moisture is a matter of routine optimization on the part of the skilled artisan" (Office Action, pp. 8-9). As noted in Seelich, fibrin matrices with a residual moisture of less than 3% are usually very rigid and brittle and hence impractical for use as implants. On the other hand, higher moisture contents are generally disadvantageous because of instability during storage (*see* Seelich, at col. 1, line 64 to col. 2, line 4). Thus, selection of the residual

moisture level is not simply a matter of routine optimization. The restriction imposed by the residual moisture level is one of the weaknesses of the prior art, which the present fibrin matrix overcomes by providing desired physical and mechanical properties, despite the low residual moisture level of less than 3%. Indeed, even at such low residual moisture level, the present fibrin matrix shows desirable physical and mechanical properties, including regular pore size, matrix flexibility, and elasticity, as measured by the tensile strength of at least 0.2 kPa and 2 mm deformation according to one embodiment (*see* p. 7, lines 9-11). Amended claim 1 underscores this beneficial feature by reciting that the matrix is "elastic." Further advantageously, the present invention allows modulation of such properties by incorporating various additives such as polysaccharides (*see* p. 19, lines 9-18; Examples 4-5), and therefore enables adjusting mechanical properties as needed for a given application.

Therefore, Seelich, which discloses a fibrin sponge containing a residual moisture of at least 3% and teaches that a lower moisture level results in a hard and brittle sponge, does not render the present claims obvious, but teaches away from the elastic fibrin matrix of the present invention having a residual moisture of less than 3%.

Likewise, none of the other cited references renders the present claims obvious.

Wadstrom discloses a tissue treatment composition, such as an adhesive composition, in the form of a viscous aqueous solution comprising fibrin or fibrinogen and a biodegradable and biocompatible polymer. As disclosed in Example 1, the components of the fibrin glue are mixed "on site," *i.e.*, on the body during surgery, using a double-syringe system to produce a viscous aqueous solution. Thus, Wadstrom relates to a solution, not to a solid composition that involves a solid-forming process, such as freeze-drying. Thus, Wadstrom simply does not relate to a freeze-dried porous matrix of the present claims.

The Examiner also states that one of ordinary skill in the art "would have had a reasonable expectation of success in adding hyaluronic acid to the sponge of Seelich" and that a skilled artisan "would have been motivated to include hyaluronic acid because Wadstrom teaches that hyaluronic acid enhances the viscosity of biodegradable matrices" (Office Action, at p. 8). However, because Wadstrom discloses only aqueous solutions and not dry solid matrices, Wadstrom relates only to the effect of hyaluronic acid in aqueous solutions wherein it enhances viscosity. As a person skilled in the art knows, hyaluronic acid has different effects on the properties of a solid matrix than on an aqueous solution, and a skilled artisan would not incorporate hyaluronic acid in a solid matrix expecting the same effects observed in an aqueous solution. Thus, it would not have been obvious, based on the

disclosure of an aqueous fibrin glue composition of Wadstrom, to include hyaluronic acid in the fibrin sponge disclosed in Seelich to reach the present freeze-dried fibrin matrix.

Wolfinbarger is cited as teaching that "freeze-dried tissue grafts contain less than about 5% residual moisture" and as supporting the Examiner's position that "it is logical to conclude that the residual moisture of said matrix before [the moisture adjusting step as taught in Seelich] must be less than 3%" (Office Action, at p. 8). As previously explained, however, selection of the level of residual moisture is not a matter of routine optimization as the Examiner states. Even though freeze-drying may result in a residual moisture level of less than 3%, a matrix with such low level of moisture is known to be hard and brittle. By contrast, the present matrix has more desirable physical and mechanical properties, despite the low residual moisture level. Thus, Wolfinbarger, alone or in combination with other cited references, does not render the present claims obvious.

The Examiner also states that "selection of pore size and spacing clearly would have been a routine matter of optimization" based on the disclosures of Li. Li relates to a porous matrix sheet made of biocompatible and bioresorbable biopolymeric material, which has at least one portion spaced from and overlapping another portion and has specific density, pore size, and spacing between overlapping portions (*see* col. 1, lines 15-23). Li generically provides that suitable biopolymeric materials include collagen, elastin, fibrin, and polysaccharide (col. 1, lines 24-26). Thus, Li simply does not relate to a freeze-dried fibrin matrix as recited in the present claims, obtained by mixing plasma proteins comprising fibrinogen and Factor XIII with thrombin and at least one anti-fibrinolytic agent in substantial absence of organic chelating agents. Further, while Li mentions fibrin as a suitable biopolymeric material, it does not provide any example of a porous matrix made with fibrin, and provides only examples of collagen matrices. Thus, not only does Li fail to disclose a fibrin matrix, but there would have been no motivation to combine Li with any of the other cited references to reach the present fibrin matrix. Li does not render the present fibrin matrix obvious, alone or in combination with the other cited references.

Accordingly, Applicants submit that none of the cited references, alone or in combination, render the present claims obvious, and respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

In view of the above, the entire application is believed to be in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues in

order to expedite the eventual allowance of the claims.

Respectfully submitted,

9-19-05

Date

Allan A. Fanucci (Reg. No. 30,256)

WINSTON & STRAWN LLP
Customer No. 28765
212-294-3311